Recent studies from our lab and others have identified extracellular PDI as an essential component of in vivo clot formation and have validated PDI as a drug target in preclinical studies. We then used high throughput screening to identify novel PDI inhibitors. One of these PDI-targeted compounds is already in phase II/III clinical trials. Yet despite this relatively rapid progress in establishing a central role for thiol isomerases in blood coagulation and moving thiol isomerase inhibitors into human studies, relatively little is known about how thiol isomerases mediated thrombus formation or how to best use thiol isomerase-targeted therapies and diagnostics in clinical practice. My talk will discuss the role PDI in thrombus formation and new approaches to its inhibition.